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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/231,422	01/14/99	CANTOR	T

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EXAMINER	
GRUN, J	
ART UNIT	**PAPER NUMBER**
1641	6

DATE MAILED: 09/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/231,422	CANTOR et al.
Examiner	**Group Art Unit**
James L. Grun, Ph.D.	1641

☒ Responsive to communication(s) filed on *14 Apr 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply w/ Sequence Disclosures

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

The disclosure is objected to because of the following informalities: page 5, line 14, "6" should be --5--; page 8, line 28, --immunogen-- is misspelled. Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application clearly fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reasons set forth below.

Applicant is advised that the CRF copy of the "Sequence Listing" filed with the communication of 14 April 2000, in response to the "Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequences And/Or Amino Acid Sequence Disclosures" or "CRF Diskette Problem Report" communications mailed 16 March 2000, required correction so that it could be entered into the database. The corrections were entered as follows: amino acid numbers were globally aligned.

However, as set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, this application clearly fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the sequences disclosed on page 7 of the specification (i.e. "hPTH" and "rat PTH" N-terminal peptides) and the sequence disclosed in Fig. 6 (PTH 7-84 fragment) are not listed in the Sequence Listing as required. It is also noted that neither sequence disclosed on page 7 is appropriately identified.

Applicant is required to provide a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, which includes each of the sequences disclosed in the specification as required by 37 CFR 1.821(c). Applicant must direct the entry of "SEQ ID NO:" identifiers for every appearance of sequences in the description or claims of the patent application. A corrected substitute copy of the "Sequence Listing" in computer readable form must be provided as required by 37 CFR 1.821(e). Applicants must also provide a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Claims 1-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-3, "the initial peptide" and "the reactive portion" lack antecedent basis.

In claims 4-11, "the amount", "the initial peptide", and "the reactive portion" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

In claims 5-6, "parathyroid...antibody" is confusing. The Examiner suggests --anti-parathyroid...antibody--.

In claims 7-9 and 11, "wPTH" and "the first antibody" are not clear and lack antecedent basis.

In claim 10, "the label or signal generating component" lacks antecedent basis.

In claim 11, "the C-terminal portion" lacks antecedent basis and is vague as to what "portion" is encompassed. The interrelationships among the antibodies and their addition to sample is not clear. Method claims should clearly set forth the various method steps in a positive, sequential manner using active tense verbs such as adding, mixing, reacting, and detecting.

In claims 12-16, "the amount", "the initial peptide", and "the reactive portion" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

In claims 15-16, "the mid-portion" and "the C-terminal" lack antecedent basis and are vague as to what "portions" are encompassed. In these claims, the interrelationships among the antibodies and their addition to sample is not clear. It is also not clear how "whole" PTH is detected in such an assay as the binding to the N-terminus appears to serve no function and label would bind and precipitate with other fragments bound by the third antibody such as the non-(1-84) PTH fragment.

In claim 16, "C-terminal...antibody" is confusing. The Examiner suggests --anti-C-terminal...antibody--.

In claim 17, "the initial peptide" and "the reactive portion" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

In claims 18-19, "the initial peptide" and "the reactive portion" lack antecedent basis.

In claim 19, "the C-terminal portion" lacks antecedent basis and is vague as to what "portion" is encompassed.

In claims 20-21, "the initial peptide" and "the reactive portion" lack antecedent basis.

In claim 21, "the C-terminal portion" lacks antecedent basis and is vague as to what "portion" is encompassed.

In claim 22, "the amount", "the initial peptide", "the reactive portion", "the peptide sequence" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

In claim 23, it is unclear from where "in the person" the levels are determined. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

In claim 24, "the person" lacks antecedent basis and it is unclear from where "in the person" the levels are determined. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-24 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Brossard et al (J. Clin. Endocrinol. Metab. 81: 3923, 1996).

Brossard et al determined levels of total parathyroid hormone (PTH) by two-site immunoassay and the proportions of that total comprising intact PTH-(1-84) and a non-(1-84) PTH fragment (by combination of high performance liquid chromatography (HPLC) with the immunoassay) in normal patients and two populations of patients having renal failure (with and without secondary hyperparathyroidism) under various calcemic conditions and compared the determinations within and among the patient populations by percentages and ratios. The reference teaches that PTH determination in renal failure is of unquestioned clinical interest and that immunoassays have greatly simplified its measurement (see e.g. page 3923).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> (c) Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-4, 6-21, and 23-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over LePage et al (Clin. Chem. 44: 805, 1998).

LePage et al used two-site immunoassays combined with HPLC to determine intact PTH and the non-(1-84) PTH fragment and to characterize the non-(1-84) PTH fragment in uremic patient sera as similar, if not identical, to the commercially available PTH-(7-84) fragment, suggest that the non-(1-84) PTH fragment is devoid of at least some of the N-terminal amino acid residues necessary for the adenylate cyclase activation activity of the intact PTH-(1-84), teach that the amino-terminal antibodies in the commercially available immunoassay kits used in the reference for intact PTH are specific for epitopes in the region of amino acid residues 14-34 of PTH (thus the cross-reactivity of the assays with the non-(1-84) PTH fragment and the ability of these assays to detect the fragment in patient sera in the reference), suggest that the fragment retains the ability to bind to PTH receptors, and suggest that a "truly" intact PTH-(1-84) could be developed using antibodies expected to be elicited by the N-terminal portion of the intact PTH-(1-84) (see e.g. page 808, col. 1-2).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited antibodies to the N-terminal portion of the intact PTH-(1-84), particularly to amino acid residues 1-6, for use in determining the intact PTH and/or non-(1-84) PTH fragment in immunoassays for analysis of PTH in uremic patients in view of the specific suggestion and expectation of success provided for such antibodies and assays in LePage et al. Substitutions of conventional alternatives for those particulars taught in the reference, such as substitution of a conventional alternative label, or using any of the conventional alternative reagent addition sequences,

such as forward, reverse, or simultaneous, for a two-site immunoassay, or using the conventional alternative of a labelled anti-C-terminal antibody with an immobilized anti-N-terminal antibody instead of immobilized anti-C-terminal antibody and labelled anti-N-terminal antibody in a two-site immunoassay, would have been well within the skill of a routineer in the art and would have been expected to function in the assays suggested in the reference for determination of "truly" intact PTH-(1-84) and/or in assays to discriminate intact PTH from the non-(1-84) PTH fragment. One would have been motivated to have provided such antibodies and assays to obviate the step of HPLC in the determinations. It would have been obvious to formulate the reagents of LePage et al into a kit since that is conventional for convenience, economy, and reproducibility.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 1-21 and 23-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over LePage et al (Clin. Chem. 44: 805, 1998) in view of Campbell.

The teachings of LePage et al are as set forth above and differ from the invention as instantly claimed in not providing monoclonal antibodies.

Campbell teaches the general procedure for the production of monoclonal antibodies (pages 3-6) and that substituting a monoclonal antibody for a polyclonal antibody in an established immunoassay "is not novel and is obvious" (page 45).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited monoclonal antibodies to the N-terminal portion of the intact PTH-(1-84), particularly to amino acid residues 1-6, for use in LePage et al because, as taught in Campbell, the substitution of monoclonal antibodies for polyclonal antibodies in an immunoassay is obvious in the art motivated by, inter alia, the well known advantage of providing a potentially unlimited source of homogeneous reagent.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 1-5, 7-10, 12-14, 17, 18, 20, and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gao et al (Clinica Chimica Acta 245: 39, 1996) in view of LePage et al (Clin. Chem. 44: 805, 1998).

Gao et al (Clinica Chimica Acta 245: 39, 1996) teach a two-site immunoassay using monoclonal antibodies for detection of "intact" and large, biologically active, N-terminal fragments of PTH. The reference differs from the invention as instantly claimed in not teaching the epitopes as instantly claimed for the two antibodies of the method.

The teachings of LePage et al are as set forth previously.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited antibodies to the N-terminal portion of the intact PTH-(1-84), particularly to amino acid residues 1-6, for use in determining the intact PTH and large N-terminal PTH

fragments in the immunoassays of Gao et al in combination with antibodies to any other non-interfering N-terminal epitope in view of the specific suggestion and expectation of success provided for such N-terminal antibodies and assays in LePage et al. Substitutions of conventional alternatives for those particulars taught in the reference, such as substitution of a conventional alternative label, or using any of the conventional alternative reagent addition sequences, such as forward, reverse, or simultaneous, for a two-site immunoassay, or using the conventional alternative of a labelled second anti-PTH antibody with an immobilized anti-N-terminal antibody instead of immobilized second anti-PTH antibody and labelled anti-N-terminal antibody in a two-site immunoassay, would have been well within the skill of a routineer in the art and would have been expected to function in the assays suggested in the references for determination of "truly" intact PTH-(1-84). One would have been motivated to have provided such antibodies and assays to determine functionally active intact PTH and N-terminal fragments as desired by Gao et al. It would have been obvious to formulate the reagents of Gao et al as modified by LePage et al into a kit since that is conventional for convenience, economy, and reproducibility.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 10, 31, and 44 of copending Application No. 09/344,639. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim assays for differentiating normal parathyroid hormone function from hyperparathyroidism by determining whole parathyroid hormone levels.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

The art made of record and not relied upon is considered pertinent to applicant's disclosure.

John et al (J. Clin. Endocrinol. Metab. 84: 4287, 1999) disclose the instant invention.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to James L. Grun, Ph.D., Technology Center 1600, Group 1640, Art Unit 1641, whose telephone number is (703) 308-3980. The Examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Long Le, SPE, can be contacted at (703) 305-3399. The fax phone numbers for official communications to Group 1640 are (703) 305-3014 or (703) 308-4242.

Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice To Comply.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

James L. Grun, Ph.D.
September 18, 2000

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641